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Ephedra—Is It Worth the Risk?

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Ephedra—Is It Worth the Risk?

Mr. Chairman, we welcome the opportunity to submit testimony for the New York State Senate Committee on Consumer Protection on the dietary supplement ephedra.

Key findings from our research:

- Ephedra and ephedrine promote modest short-term weight loss; their long-term effect is unknown.
- Ephedrine plus caffeine moderately boosts performance for fit young men; there is no evidence that ephedra or ephedrine improves long-term physical performance of athletes or would work for the general public.
- Ephedra and ephedrine increase the risk of nausea, vomiting, jitteriness, and palpitations.
- These products may be linked to catastrophic events such as sudden death, heart attack, or stroke.

Products that contain the herb ephedra have been promoted and used in the United States since the 1980s to increase weight loss and enhance athletic performance. Yet despite manufacturers' claims, little research has been done to assess whether the products are safe, and the research studies that have been done have been too small to allow any firm conclusions to be drawn.

The questionable effectiveness of these products might not have raised public concern, had the U.S. Food and Drug Administration (FDA) and major manufacturers of ephedra-containing products not become the targets of growing numbers of consumer complaints in the late 1990s. Reports of adverse events, including serious side effects and even deaths, many in apparently healthy young people, began increasing during this time. Prominent among the victims have been several college and professional athletes. Thus, in recent years, several major consumer health groups have called on the FDA to ban sales of ephedra-containing products.

The FDA classifies products containing herbal ephedra as dietary supplements, which are regulated by the Dietary Supplement Health and Education Act of 1994 (DSHEA). Under DSHEA, dietary supplements are generally "presumed safe"; thus, manufacturers are required only to notify the FDA of their intent to market new products but are not required to establish the safety or effectiveness of their products. Once a dietary supplement is on the market, the FDA can restrict its use or ban sales of the product only if it can demonstrate convincingly that the product is unsafe.

As complaints continued to mount, the U.S. Department of Health and Human Services called for a review of all the evidence, turning to the Southern California Evidence-Based Practice Center (SCEPC), based at RAND. The SCEPC is one of 13 federally sponsored evidence-based

This testimony summarizes RAND research reported in the following publications:

Shekelle P, Morton SC, Maglione M, Hardy M, Suttorp M, Roth E, Jungvig L, Mojica W, Gagné J, Rhodes S, McKinnon E, and Newberry S. *Ephedra and Ephedrine for Weight Loss and Athletic Performance Enhancement: Clinical Efficacy and Side Effects*. Prepared for the Agency for Healthcare Research and Quality, 2003. Full text available at www.ahrq.gov/clinic/ephedinv.htm.

Shekelle P, Morton SC, Maglione M, Hardy M, Mojica W, Suttorp M, Rhodes S, Jungvig L, and Gagné J. Efficacy and Safety of Ephedra and Ephedrine for Weight Loss and Athletic Performance: A Meta-Analysis. *JAMA*. March 26, 2003. Vol. 289, No. 12, pp. 1537-45.

practice centers nationwide that specializes in seeking answers to important health care questions through assessing and synthesizing the evidence from large numbers of research studies.

Statistically combining the findings of many similar studies increases researchers' confidence that small apparent differences in the effects of two treatments are in fact real. We were asked to review all studies of ephedra-containing dietary supplements conducted to date, to assess whether the substance actually lives up to manufacturers' claims and whether the supplements are safe for the general population, or whether they are in fact responsible for the adverse effects that have been attributed to them.

What We Did (and Why)

Our assessment of the evidence was guided by a distinguished panel of technical experts, both basic scientists and clinicians. This group included cardiologists, exercise physiologists, pharmacologists, and toxicologists, as well as specialists in obesity, nutrition, and the science of pharmacognosy. The technical expert panel recommended that we also review studies of over-the-counter medications that contain the chemical ephedrine, presumed to be the primary active ingredient of ephedra (ephedrine-containing products are regulated as pharmaceuticals, not as dietary supplements). In addition, many ephedra-containing supplements also include herbs that contain caffeine, and products that contain ephedrine often include caffeine. Because caffeine is believed to have effects that are similar to ephedrine, such combinations could potentially be more powerful than either substance alone. Thus, we were also asked to review the evidence for the effectiveness and safety of supplements that combine ephedra and caffeine as well as ephedrine and caffeine-containing products.

To assess the evidence for the effectiveness of ephedra and ephedrine in weight loss and athletic performance, we performed an exhaustive search and review of the medical research "literature" using the well-accepted procedures of evidence-based medicine. The literature review was conducted by our staff with the assistance of several clinical experts.

Only controlled clinical trials and randomized controlled trials of effectiveness—that is, studies that satisfied a strict set of quality criteria—were included in our analysis. Randomized controlled trials (RCT) are clinical trials in which participants are assigned randomly to one of two or more treatment groups. Controlled clinical trials are those in which participants are assigned to a treatment group using a semi-random procedure (such as a participant's date of birth, a patient identification number, or the order of enrollment). In all, we reviewed the results of 52 clinical trials that measured the effects of ephedra or ephedrine on weight loss and athletic performance. Most of these studies included one group of participants who were randomly chosen to receive only a placebo (an inactive dummy pill). This type of study maximizes the likelihood that any differences found between the groups taking the test supplement and those taking the placebo are real, not due to chance or bias.

What We Found

Studies of Weight Loss. Studies of weight loss usually measure the weight lost over the course of the study, the weight lost per month, or the proportion of an individual's original weight that was lost. For each group of studies that made the same comparisons (for example, all studies that compared the effects of ephedra and herbal caffeine on weight loss with the effects of a placebo),

we combined the results of all studies in that group, using a statistical technique called meta-analysis, and calculated the average total weight lost as well as the average lost per month.

Over the short term (four to six months), ephedrine, ephedrine plus caffeine, and supplements containing ephedra or ephedra plus caffeine promoted modest increases in weight loss, about two pounds per month more than the weight loss of persons taking the placebo. Products containing caffeine seemed to promote slightly more weight loss than those containing only ephedrine. However, none of the studies lasted longer than six months, far less than the twelve months researchers consider the minimum necessary to establish the value of a weight loss product (studies that lasted less than two months were excluded from our analysis because two months is simply too short a time to assess a meaningful change in weight).

Studies of Athletic Performance. We found no studies that assessed the effects of ephedra-containing dietary supplements on athletic performance. Thus we analyzed only studies of products containing ephedrine or ephedrine plus caffeine—seven studies in all. No two studies were judged similar enough in design to combine their results: Measures of athletic performance varied widely from one study to another. As a result, our conclusions regarding the effects of ephedrine on athletic performance are based on a nonquantitative synthesis of the research rather than on meta-analysis. In addition, no study looked at long-term changes in performance.

Our analysis found that one-time use of ephedrine-containing products seems to enhance immediate physical performance, but only when taken in combination with caffeine. These results, too, must be interpreted with caution. The studies assessed performance immediately after a single dose; none of the studies examined the type of chronic, long-term use typical of consumers of these products. What's more, the study participants—all young, fit males—may not be typical of the average consumer.

Studies of Safety. To assess the safety of ephedra- and ephedrine-containing products, we reviewed four sources for reports of adverse events.

First, we reviewed the clinical trials included in our analyses of weight loss and athletic performance, most of which reported adverse events for both treatment and placebo groups. The trials contained no reports of very serious adverse events (such as death and cardiovascular events). This is not surprising, considering that the occurrence of such events is likely to be quite rare (less than one in a thousand users) and the clinical trials included only a few thousand people. However, we found a two- to threefold increase in the occurrence of nausea, vomiting, anxiety, autonomic hyperactivity, and palpitations, and a trend toward an increase in headaches.

We also reviewed descriptions of medical cases published in peer-reviewed journals. This review identified 70 reports of adverse events, including heart attacks, strokes, and serious psychiatric problems. We then obtained all adverse-event reports submitted to the FDA prior to September 2001 that were associated with the use of ephedra or ephedrine-containing products and for which records existed: more than 1,500 adverse-event reports on ephedra and 125 on products containing ephedrine. Finally, we analyzed more than 18,000 adverse-event reports received by one of the largest U.S. manufacturers of ephedra-containing dietary supplements. These reports had been turned over to the FDA at the request of the U.S. Department of Justice. Based on the

available evidence, these reports were classified as "sentinel events," "possible sentinel events," or lacking in sufficient evidence (see Table 1).

The majority of the adverse-event reports lacked sufficient information to demonstrate a connection between the event and use of ephedra or ephedrine. Nevertheless, we did identify a number of reports of sentinel and possible sentinel events, including death, stroke, myocardial infarction (heart attack), ventricular tachycardia/fibrillation, cardiac arrest, pulmonary arrest, transient ischemic attack, brain hemorrhage, seizure, psychiatric symptoms, and gastrointestinal symptoms (see Table 2). Of particular concern is that half the sentinel events occurred in apparently healthy people under the age of 30.

What Should Be Done?

The studies we reviewed suggest that ephedra- and ephedrine-containing products may be modestly effective in promoting weight loss, but the evidence on enhancing athletic performance is not definitive. However, the use of ephedra or ephedrine does cause an increase in jitteriness, mood changes, palpitations, nausea, and vomiting. Moreover, the adverse-event reports raise serious concerns about the safety of ephedra and ephedrine products.

Table 1. Criteria for Classifying Adverse Events

Sentinel Event	Possible Sentinel Event
Documentation of the adverse event	Documentation of the adverse event
Documentation (by report or toxicology exam) that ephedra or ephedrine was consumed within the prior 24 hours*	Documentation (by report or toxicology exam) that ephedra or ephedrine was consumed within the prior 24 hours*
Documentation that other possible causes of the event were evaluated and excluded	Other potential causes exist or were not effectively excluded

*The 24-hour requirement was not applied to reports of psychiatric events because these events are believed to result from prolonged use.

Table 2. Adverse Events Associated with Ephedra and Ephedrine

Event	Number of Events	Number of Sentinel Events	Number of Possible Sentinel Events
Death	84	5	12
Myocardial infarction (heart attack)	26	5	7
Other cardiac	30	0	3
Cerebrovascular event (stroke)	56	11	12
Seizure	40	4	7
Other neurological	8	0	1
Psychiatric event	91	8	8